Anaphylaxis

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Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: http://www.tandfonline.com/loi/ierm20

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To cite this article: Sangeeta Dhami & Aziz Sheikh (2017): Anaphylaxis: epidemiology, aetiology and relevance for the clinic, Expert Review of Clinical Immunology, DOI: 10.1080/1744666X.2017.1334552

To link to this article: http://dx.doi.org/10.1080/1744666X.2017.1334552

Accepted author version posted online: 31 May 2017.

Publisher: Taylor & Francis

Journal: *Expert Review of Clinical Immunology*

DOI: 10.1080/1744666X.2017.1334552

Anaphylaxis: epidemiology, aetiology and relevance for the clinic

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Abstract

Introduction

Anaphylaxis is responsible for considerable morbidity and it may in some cases prove fatal.

Areas covered

This review summarises the findings from recent studies on the epidemiology and aetiology of anaphylaxis and draws on the insights from this work and recent international guidelines to consider the implications for clinical care. Acute management of anaphylaxis is centred on early recognition, treatment with adrenaline (epinephrine) and other essential life-support measures. The importance of longer-term care of patients with a history of or at risk of anaphylaxis are also considered with a view to minimising the risk of further reactions and decreasing the severity and impact of these reactions. Tailored individual

anaphylaxis management plans should be a routine component of this longer-term care with provision of adrenaline auto-injectors to those at risk of further episodes of anaphylaxis. More generally, there is a need to ensure that there are standard protocols in place to ensure that risks of triggering anaphylaxis are minimised and appropriate acute and long-term care are provided if reactions occur.

Expert commentary

It is important to be aware that anaphylaxis may occur in patients of any age, sex or ethnicity. Early recognition and prompt treatment with adrenaline are potentially life-saving. Careful assessment of risk and appropriate long-term management are key to improving long-term outcomes in those at risk of repeat episodes of anaphylaxis.

Keywords: adrenaline; allergy; anaphylaxis; hypersensitivity; guidelines; incidence; self-management

1. Introduction

Anaphylaxis is an acute, potentially life-threatening systemic hypersensitivity reaction. This article aims to provide a synopsis of the evidence on its epidemiology, aetiology and clinical management. We draw in particular on the findings from international guidelines to provide recommendations on both the acute and longer-term management of anaphylaxis.[1 2 3] In so doing, our focus is on providing information and insights that will be of direct relevance both in the context of providing effective emergency care and to reduce the risk of further reactions. We begin by reviewing definitions and the key clinical features of anaphylaxis.

2. Defining anaphylaxis

Anaphylaxis has been defined as a *"severe, life-threatening generalized or systemic hypersensitivity reaction,"*[4 5] which may prove fatal through cardiovascular and/or respiratory compromise. Reactions are most commonly IgE-mediated involving allergen exposure, which triggers release of a range of inflammatory mediators from mast cells and basophils. Other non-IgE mediated pathophysiological mechanisms have also been described, particularly in relation to drug triggered anaphylaxis.[6 7] Previously, there was a distinction made between what were sometimes described as IgE-mediated 'anaphylactic' reactions and non-IgE-mediated 'anaphylactoid' reactions; however, given that the emergency management of these reactions is identical this nomenclature is no longer in clinical use. In keeping with this convention, we will use the term anaphylaxis in the remainder of this article.

3. Clinical features

The signs and symptoms of anaphylaxis are wide-ranging, involving multiple organ systems (see Box 1). The vast majority of reactions have an acute onset – typically within seconds or minutes – but slower courses of reaction over an hour or two may sometimes occur. This can lead to difficulty and delay in the prompt diagnosis of anaphylaxis, particularly with the first episode, as a range of differential diagnoses may need to be considered (see Box 2). Signs and symptoms suggesting compromise of either the respiratory or cardiovascular system or both should be particularly noted as fatalities arise from failure of one or both of these systems.[8] It should be noted that the presence of shock is not mandatory for the diagnosis of anaphylaxis; indeed, it is absent in most cases of anaphylaxis triggered by foods.[9] Biphasic or protracted late-phase reactions may occur some hours after the initial reaction.

Box 1: Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   c. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Reproduced with permission from John Wiley and sons from Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology[1] originally from Sampson et al [10] PEF, Peak expiratory flow; BP, blood pressure.*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 [2 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.*

Box 2: Differential diagnoses of anaphylaxis

Skin or mucosal	• Chronic remittent or physical urticaria and angioedema • Pollen-food syndrome
Respiratory diseases	• Acute laryngotracheitis • Tracheal or bronchial obstruction (e.g. foreign substances, vocal cord dysfunction) • Status asthmaticus (without involvement of other organs)
Cardiovascular diseases	• Vasovagal syncope • Pulmonary embolism • Myocardial infarction • Cardiac arrhythmias • Hypertensive crisis • Cardiogenic shock
Pharmacological or toxic reactions	• Ethanol • Histamine (e.g. scombroid fish poisoning) • Opiates
Neuropsychiatric diseases	• Hyperventilation syndrome • Anxiety and panic disorder • Somatoform disorder (e.g. psychogenic dyspnea, vocal cord dysfunction) • Dissociative disorder and conversion (e.g. globus hystericus) • Epilepsy • Cerebrovascular event • Psychoses • Artifact (factitious disorder) • Hoigné's syndrome • Coma (e.g. metabolic, traumatic)

Endocrinological diseases	• Hypoglycemia • Thyrotoxic crisis • Carcinoid syndrome • Vasointestinal polypeptide tumours • Pheochromocytoma

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4. Epidemiology

The epidemiology of anaphylaxis is difficult to characterise reliably because of the acute and transient nature of the reactions and the associated challenges in establishing prospective studies.[11] [12] Nonetheless, a number of studies have been undertaken over the last two decades. A systematic review conducted in 2013 estimated that the incidence rates for anaphylaxis in Europe from any cause ranged from 1.5 to 7.9 per 100,000 person years with an estimated 1 in 300 people experiencing anaphylaxis at some point in their lives.[13] The lifetime prevalence of anaphylaxis in the UK increased from 50 to 76 per 100 000 from 2001 to 2005.[14]

There have now been a number of studies investigating hospitalisations due to anaphylaxis in the UK, USA and Australia, these suggesting that the incidence of anaphylaxis may be increasing.[15] [16] [17] More detailed analyses of these data suggest that the most marked increase is in the under-five age group, which may be related to the increasing prevalence of food-allergy.[18] A recent time trend study conducted in Australia between 2011 to 2012 supported this, finding that anaphylaxis was increasing most in the 0-4 age group followed by children aged 5-14 years.[17]

This increased incidence in anaphylaxis has not however been associated with a concomitant increased fatality rate. Data from a large US epidemiological study showed the case fatality rate remained steady at 0.3%. Data from the UK national anaphylaxis database found that between 1992 and 2012 there was no increase in deaths from anaphylaxis.[12, 19]

The risk of recurrence of anaphylaxis is poorly studied, but a study from Australia found that one in 12 patients will experience a recurrent episode of anaphylaxis within a year and an estimated one in 50 will require treatment with adrenaline (epinephrine) and/or hospitalisation. [20] This study also investigated factors that contributed to the recurrent reactions and found that accidental ingestion of peanut/tree nut was the greatest risk factor. The combination of wheat sensitivity and exercise was also found to be an important risk factor.

Important relevant epidemiological definitions have been summarised in Box 3.

Box 3: Epidemiological definitions

Incidence: The number of new cases of anaphylaxis that occur during a given period in a defined population. Incidence is divided into:

- Incidence rate: The number of new cases of anaphylaxis that occur during a defined period per unit person-time.
- Cumulative incidence: The number of new cases of anaphylaxis that occur during a given period per the population at risk.

Prevalence: The proportion of a defined population known to have experienced anaphylaxis. Care is required in defining the appropriate denominator. This epidemiological measure is further divided into:

- Point prevalence: the proportion of the population that has experienced anaphylaxis at a specific time
- Period prevalence: the proportion of the population that has experienced anaphylaxis during a given period
- Lifetime prevalence: the proportion of the population that at some point in their life will have experienced anaphylaxis.

Case fatality rate: The proportion of cases of anaphylaxis that proves fatal (usually defined within a time period). This is also sometimes known as the case fatality ratio.

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5. Aetiology

There are many potential risk factors, triggers and co-factors of anaphylaxis, the most important of which are discussed here. It is important to note that these aetiological factors may vary with age and an

appreciation of these chronological changes can prove very helpful in securing the diagnosis of anaphylaxis.[22]

5.1 Risk factors

Genetic factors can predispose certain individuals to developing atopy and certain associated allergic disorders – for example, food allergy – which may increase the risk of anaphylaxis.[23] Other allergic conditions such as drug and venom allergy can also manifest as anaphylaxis, but these do not appear to have an inherited basis.

Environmental exposures can in some cases result in allergy and also be associated with an increased risk of anaphylaxis.[24] Occupational groups that may be affected include beekeepers who are as a result at increased risk of venom allergy, healthcare professionals exposed to natural rubber latex and workers exposed to fruits and vegetables, drugs and chemicals.

5.2 Triggers

Foods

Many foods can induce anaphylaxis, the most common of which are cow's milk, hens eggs, peanuts, tree nuts, fish, shell-fish, soy and wheat. The relative importance of these can however vary by geography and local dietary patterns.[25] Anaphylaxis to food is most common in children, but can occur in people of any age.

Insect stings

Hymenoptera allergy is an important cause of anaphylaxis and is occasionally responsible for fatalities. The most common stinging insects include bees, wasps, polistes, hornets and fire ants. Venom allergy fatalities are more common in adults than in children.[26] [27]

Drugs/pharmacological agents

Any drug can cause anaphylaxis, but some classes of drugs are known to illicit drug reactions more frequently. Further, parental administration can increase the risk of a reaction to, for example, penicillin and this mode of administration can also increase the severity of a reaction.[28] The most common drugs causing allergic reactions include:

- Antibiotics such as penicillin, sulphonamides and cephalosporins

- Non-steroidal anti-inflammatories (NSAIDs)
- Chemotherapy
- Mono-clonal antibodies
- Contrast media.[29]

Other triggers

There are a number of other triggers, including:

- Natural rubber latex: This was an important cause of allergy particularly in healthcare workers due to the use of rubber gloves, but this has reduced in countries where latex gloves are no longer used. Allergic reactions can range from mild to severe including anaphylaxis which is more common on repeated exposure to the allergen.
- Exercise-induced anaphylaxis: This is a relatively rare cause of anaphylaxis and somewhat unpredictable as to the amount or intensity of exercise needed to trigger a reaction. The frequency of attacks can range from single to multiple in one year.[30]

5.3 Co-factors

Particular conditions experienced by an individual, also sometimes known as co-factors, may increase the risk of developing anaphylaxis and/or a poorer outcome from a reaction (Box 4). For example, children with food allergy who have co-existent asthma are at increased risk of fatal respiratory compromise. Similarly, adults with co-existent cardiovascular disease have an increased risk of life-threatening cardiovascular shock if they experience anaphylaxis.

External factors may also be important, which can make individuals more susceptible to developing anaphylaxis such as exercise, alcohol, drugs, infection and stress.[31] These are sometimes also called augmentation factors.

Box 4: Examples of risk-and co-factors of anaphylaxis

Lifestyle factors	• Physical exertion • Alcohol
Drugs	• NSAIDs • ACE inhibitors • β-blockers

Patient specific factors	• Adolescence, advanced age and sex • Infections • Hormonal status • Psychogenic stress
Pre-existing conditions	• Asthma and other IgE-dependent diseases • Cardiovascular disease • Mastocytosis and/or increased basal tryptase

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6. Implications for clinical care

A number of guidelines have been developed to support frontline clinicians to consistently deliver high quality anaphylaxis care.[1 2 3] These are needed as evidence suggests that the management of anaphylaxis remains sub-optimal.[32] Clinicians and departments should familiarise themselves with at least one guideline and have protocols in place to ensure that the key recommendations are implemented. Regular training should be provided to all staff who will be involved in delivering care to these patients. Audits should be performed to evaluate the care provided.

6.1 Acute management

Prompt recognition and diagnosis of anaphylaxis is essential. The treatments used can be divided into first- and second-line interventions.

First-line intervention

All guidelines agree that the first-line treatment for anaphylaxis is adrenaline,[33] which should be administered intramuscularly into the mid outer thigh without delay.[29 34] Fatality register studies have found that a delay in the administration of adrenaline increases the risk of death; also of relevance is that predicting the severity of a reaction from its initial manifestations may prove difficult.[35 36] Adrenaline may need to be repeated at five minute intervals if the patient is not improving or symptoms recur. The easiest form of administering adrenaline is with a pre-loaded auto-injector. If adrenaline is drawn up it should be administered at a dose of 1mg/ml at a dose of 0.01ml/kg of body weight to a maximum total dose of 0.5ml.[5] Intravenous adrenaline should only be administered by those with experience in this – typically intensive care unit (ICU) clinicians – and with appropriate facilities for cardiac monitoring.

The safety profile of adrenaline is excellent and prompt administration can be life-saving. Even in the elderly and patients with cardiovascular disease the benefits of using adrenaline far out-weigh the risks in an anaphylactic reaction.[2] There are therefore no absolute contraindications to the use of adrenaline.

Second-line interventions

Second-line treatment involves removal of the trigger if possible – for example, a bee sting, food from the mouth or discontinuing IV medication. It is important to lie the patient down unless they are experiencing respiratory difficulty in which case they should be sitting. This is important to minimise the risk of empty ventricle syndrome. In addition to the adrenaline, which as noted above may need to be repeated, H_1-anti-histamines, corticosteroids and beta-$_2$ agonists should be considered. Use of second-line agents are not life-saving, but may reduce other features of anaphylaxis and these may also reduce the risk of biphasic and protracted reactions.[37] [38] Patients should then be monitored for up to 12 hours after recovery in case they develop a biphasic reaction, where symptoms initially resolve and then return.[39] Patients should be discharged with an adrenaline auto-injector and advise on when and how to use it if there is a risk of a recurrent reaction.

Box 5: Checklist for the acute management of anaphylaxis

1. Stay with patient
2. Look for signs of anaphylaxis
3. Administer adrenaline if signs of anaphylaxis
4. Repeat adrenaline as necessary
5. Other treatments as indicated (e.g. oxygen, beta-2 agonist, fluids, antihistamine, corticosteroid)
6. Look for trigger (e.g. food, drug, venom)
Adrenaline is effective for all symptoms

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6.2 Longer-term management

Referral and allergen avoidance

All patients with a first episode of anaphylaxis should be referred to a specialist for further evaluation. The mainstay of longer-term care is identification of the trigger and any co-factors and providing detailed advice on how to avoid these allergic and/or other triggers. This will typically involve skin prick testing and/or specific-IgE testing in suspected allergic reactions, and this may in some case also involve challenge tests in carefully controlled and monitored clinical settings. All those at risk of further anaphylaxis should be issued an adrenaline auto-injector pen and it is vitally important that they have

received training on when and how to use their auto-injector. Training devices are readily available from the manufacturers and training videos are freely accessible.[40] [41]

Managing co-existent disease

It is important to ensure that any co-existent asthma and/or cardiovascular disease is/are optimally controlled as uncontrolled disease puts patients at increased risk of poor outcomes. Avoid prescribing angiotensin converting enzyme (ACE) inhibitors and beta-blockers. This is because ACE inhibitors prevent the normal physiological response of angiotensin release to compensate for fluid loss which often occurs in anaphylactic shock hence compounding the effects of the reaction.[42] Patients on beta-blockers may be at an increased risk of a more severe anaphylaxis as beta-blockers, whether given topically or orally, can prevent the effect of adrenaline at the beta-adrenergic receptor thus reducing its effect [43] [44]

Information and communication

Advise should be given on wearing relevant identification jewellery e.g. MedicAlert (www.medicalert.co.uk) and contact information needs to be provided for anaphylaxis patient support groups. We advise that patients/parents inform work/carers/schools, etc. so that they can arrange to have access to adrenaline auto-injectors for the named patient. Clearly noting the diagnosis of 'Anaphylaxis' in all paper and electronic health records is important to ensure effective communication across care transitions. It is particularly important that all staff involved in potentially high-risk situations such as vaccinations, anaesthesia and immunotherapy are trained in the recognition and management of anaphylaxis.

Anaphylaxis management plans

The patient/carer should be provided with a tailored anaphylaxis management plan (see Box 6), which includes instructions on managing allergy in different contexts. Relevant information may include:

- Allergen avoidance measures (where possible)
- How to recognise anaphylaxis
- When to use their adrenaline auto-injector
- How to use their adrenaline auto-injector
- What to do next.

Box 6: Example of an individualised management plan

If you think you/your child/other are having an anaphylactic reaction after possible contact with an allergic trigger. or after possible contact with an allergic trigger, any of the following symptoms may indicate that you/your child/other is experiencing an anaphylactic reaction:

- Airway problems: swelling of tongue, swelling/tightness in the throat, difficulty swallowing, difficulty talking and/or hoarse voice
- Breathing problems: difficulty breathing, noisy breathing, wheeze and/or persistent cough
- Consciousness: feeling faint, dizziness, confused state or loss of consciousness/pale and floppy (young children)

Then:

1. Immediately administer adrenaline auto-injector into the upper outer thigh
2. Call an ambulance stating that the patient is having an anaphylactic reaction
3. Lay person having the reaction down (with legs up if possible); if there is difficulty in breathing, allow them to sit up but not stand
4. If no improvement after 5 minutes, administer a second adrenaline auto-injector.

When in doubt, administer the adrenaline auto-injector.

This is only one example of an anaphylaxis action plan. The plan should be individualized, for example, patients with previous rapid onset life-threatening anaphylaxis may be instructed to use their self-injectable adrenaline earlier in the development of any subsequent allergic reaction

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Allergen immunotherapy

Allergen immunotherapy (AIT) is a potential disease-modifying treatment that can be used for venom allergy and food allergy, with encouraging results.[45] [46] This mode of treatment is most well established for venom allergy. Patients who have experienced anaphylaxis will often feel anxious regarding a recurrence and have considerable psychological morbidity which is further heightened from the continuous carriage of an adrenaline auto-injector. Venom immunotherapy has been shown to improve patient's quality of life.[47]

AIT for food allergy is a developing area and offers the first potentially curative approach to managing this condition. Foods for which this is available and have been shown to be effective in terms of desensitisation (i.e. the ability to safely consume foods containing the allergen in question whilst on AIT are cow's milk, hens eggs and peanut.[46] It remains to be determined whether tolerance (i.e. the ability to consume the foods in question post-discontinuation of AIT) can be induced. This therapy is most effective in children rather than adults and needs to be conducted by specialists with full resuscitative equipment available. The risk of systemic side-effects is increased by taking AIT so specialist input in selecting the appropriate patients is required.

Follow-up

Regular follow-up should be considered to reassess risk, review the need for auto-injector training and in children the dose of adrenaline, optimise treatment and ensure appropriate care co-ordination. A summary of the long-term management of anaphylaxis can be found in Box 7.

Box 7: Summary of the long term management of anaphylaxis

Provision of individualized management plan written clearly in simple, non-medical language; it should include: »personal identification data: name and address; contact details of the parents, guardian or next of kin, allergist, family doctor and the local ambulance service; and preferably a photograph »clear identification of the source of the allergens to be avoided and allergen avoidance advice »clear identification of any non-allergen triggers or cofactors, such as exercise, and avoidance advice »anaphylaxis emergency action plan Copy of plan should be kept by the patient, any caregivers, school staff and family doctor.

- Provision of emergency kit with copy of anaphylaxis emergency action plan and medications for self-treatment, e.g. »adrenaline auto-injector for treating anaphylaxis, where appropriate »fast acting, non-sedating, antihistamine for treating cutaneous allergic reactions, where appropriate
- Venom immunotherapy and desensitisation in drug allergy as appropriate.
- Training of patients and caregivers, this should include: »instructions on appropriate allergen avoidance measures, including consultation with an allergy dietitian, where appropriate »instructions on prompt recognition of symptoms of anaphylaxis »training on when and how to use an adrenaline auto-injector, where appropriate reinforcement with revision at regular yearly intervals
- Psychological support as required
- Implementation of the patient's management plan in the community (e.g. nursery, school)

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7. Conclusions

Anaphylaxis is a condition associated with considerable morbidity and it may on occasions also prove fatal.

8. Expert commentary: Much of this morbidity and mortality is potentially preventable through earlier recognition, prompt emergency treatment with adrenaline and proactively assessing and taking steps to reduce the risk of further reactions. Evidence-based guidelines now exist to support clinicians to provide consistent high quality acute and long-term anaphylaxis care.

9. 5-year view: We envisage some further developments in the underlying evidence base to help risk stratification and substantial additional developments in work supporting the implementation of recommendations from recent guidelines into routine care.

10. Key issues

- Anaphylaxis is responsible for considerable morbidity and it may in some cases prove fatal.
- Acute management of anaphylaxis is centred on early recognition, prompt treatment with adrenaline (epinephrine) and other essential life-support measures.
- The importance of longer-term care of patients with a history of and/or those at risk of anaphylaxis need to be considered with a view to minimising the risk of further reactions and decreasing the severity and impact of any reactions that do occur.
- There needs to be focused efforts to translate the recommendations from recent evidence-based anaphylaxis guidelines into routine clinical care.

Key references

1. **Most recently published guidelines on the management of anaphylaxis**
   Muraro A, Roberts G, Worm M, Bilo MB, Brockow K,Fernandez Rivas M et al on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group, Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology Allergy Volume 69, Issue 8, Version of Record online: 9 JUN 2014
2. **Concise guide to the evidence based management of anaphylaxis**
   Simons FE, Sheikh A. Evidence based management of anaphylaxis. Allergy 2007; 62;827-829
3. **Systematic review on the epidemiology of anaphylaxis**
   Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, Roberts G, Worm M, Bilò MB, Cardona V, Dubois AE, Dunn Galvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggemann B, Santos AF, Vlieg-Boerstra BJ, Zolkipli ZQ, Sheikh A; EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013 Nov;68(11):1353-61. doi: 10.1111/all.12272. Epub 2013 Oct 14
4. **Systematic review on the management of anaphylaxis**
   Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò MB, Cardona V et al; EAACI Food Allergy and Anaphylaxis Guidelines Group Management of anaphylaxis: a systematic review. Allergy. 2014 Feb;69(2):168-75. doi: 10.1111/all.12318. Epub 2013 Nov 20

Funding

No funding to declare

Declaration of interest

S Dhami declares involvement in the development of the EAACI Anaphylaxis systematic review and guidelines. A Sheikh declares involvement in the EAACI anaphylaxis systematic reviews and guideline development and involvement in the UK Resuscitation council anaphylaxis guidelines development. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

[1] Muraro A, Roberts G, Worm M, Bilo MB, Brockow K,Fernandez Rivas M et al on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group, Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology Allergy Volume 69, Issue 8, Version of Record online: 9 JUN 2014

[2] Simons FER, Ardusso LRF, Bilo MB, ElGamal YM, Ledford DK, Ring J et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. J Allergy Clin Immunol 2011;127:587–593

[3] Working Group of the Resuscitation Council (UK) Emergency treatment of anaphylactic reactions Guidelines for healthcare providers January 2008 update 2016 https://www.resus.org.uk/anaphylaxis/emergency-treatment-of-anaphylactic-reactions/

[4] Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier B, Lockey RF et al. A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of World Allergy Organization. J Allergy Clin Immunol 2004, 113:832-836.

[5] Muraro A, Roberts G, Clark A, Eigenmann PA, Halken S, Lack G et al. EAACI Task Force on Anaphylaxis in Children. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. Allergy 2007, 62(8):857-871

[6] Lee, JK; Vadas, P (July 2011). "Anaphylaxis: mechanisms and management". Clinical and Experimental Allergy. 41 (7): 923–38. doi:10.1111/j.1365-2222.2011.03779.x. PMID 21668816.

[7] Ring, J; Behrendt, H; de Weck, A (2010). "History and classification of anaphylaxis" (PDF). Chemical Immunology and Allergy. Chemical Immunology and Allergy. 95: 1–11. doi:10.1159/000315934. ISBN 978-3-8055-9441-7. PMID 20519878.

[8] Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation 2008;77:157-69

[9] Sheikh A. Emergency management of anaphylaxis: current pharmacotherapy and future directions Expert Opin. Pharmacother. 2013 May; 14(7):827-30. doi: 10.1517/14656566.2013.781583. Epub 2013 Mar 19.

[10] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117:391–
397.

[11] Simons FE, Sheikh A. Evidence based management of anaphylaxis. Allergy 2007; 62;827-829.

[12] Lieberman P1, Camargo CA Jr, Bohlke K, Jick H, Miller RL, Sheikh A, Simons FE. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol. 2006 Nov;97(5):596-602.

[13] Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, Roberts G, Worm M, Bilò MB, Cardona V, Dubois AE, Dunn Galvin A, Eigenmann P, Fernandez-Rivas M, Halken S, Lack G, Niggemann B, Santos AF, Vlieg-Boerstra BJ, Zolkipli ZQ, Sheikh A; EAACI Food Allergy and Anaphylaxis Group. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013 Nov;68(11):1353-61. doi: 10.1111/all.12272. Epub 2013 Oct 14.

[14] Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. J R Soc Med 2008; 101:139–143

[15] Sheikh A, Alves B Hospital admissions for acute anaphylaxis: time trend study. BMJv.320(7247); 2000 May 27PMC27386

[16] Ma l, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. JACI **April 2014**Volume 133, Issue 4, Pages 1075–
1083 http://dx.doi.org/10.1016/j.jaci.2013.10.029

[17] Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012 J Allergy Clin Immunol. 2015 Aug; 136(2):367-75. doi: 10.1016/j.jaci.2015.05.009. Epub 2015 Jul 14

[18] Koplin JJ, Martin PE, Allen KJ. An update on epidemiology of anaphylaxis in children and adults. Curr Opin Allergy Clin Immunol. 2011 Oct;11(5):492-6. doi: 10.1097/ACI.0b013e32834a41a1.

[19] Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, Pumphrey R, Boyle RJ. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012.

[20] Mullins RJ. Anaphylaxis: risk factors for recurrence. Clin Exp Allergy. 2003 Aug;33(8):1033-40.

[21] Last JM, editor. A dictionary of epidemiology. 4th ed. New York, NY: Oxford University Press, 2000.

[22] Alves B, Sheikh A. Age specific aetiology of anaphylaxis Arch Dis Child. 2001 Oct;85(4):348.

[23] Lieberman P. Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol 2008;8:316–320.

[24] Quirce S, Fiandor A. How should occupational anaphylaxis be investigated and managed? Curr Opin Allergy Clin Immunol. 2016 Apr;16(2):86-92. doi: 10.1097/ACI.0000000000000241.

[25] Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A and on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group Prevalence of common food allergies in Europe: a systematic review and meta-analysis Allergy. 2014 Aug;69(8):992-1007. doi: 10.1111/all.12423. Epub 2014 May 10

[26] Golden DB. Anaphylaxis to insect stings. Immunol Allergy Clin N Am. 2015;35(2):287–302. doi:10.1016/j.iac.2015.01.007.

[27] Novembre E, Cianferoni A, Bernardini RA, Ingargiola A, Lombardi E, Vierucci A. Epidemiology of insect venom sensitivity in children and its correlation to clinical and atopic features. Clin Exp Allergy. 1998;28:834–8.

[28] Lockey, R F. Anaphylaxis:Synopsis Posted: September 2012 (Updated; originally posted July 2004) http://www.worldallergy.org/professional/allergic_diseases_center/anaphylaxis/anaphylaxissynopsis.php

[29] Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò MB, Cardona V et al; EAACI Food Allergy and Anaphylaxis Guidelines Group Management of anaphylaxis: a systematic review. Allergy. 2014 Feb;69(2):168-75. doi: 10.1111/all.12318. Epub 2013 Nov 20.

[30] Shadick NA, Liang MH, Partridge AJ, Bingham III CO, Wright E, Fossel AH, Sheffer ALThe natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study.
J Allergy Clin Immunol. 1999 Jul; 104(1):123-7.

[31]Worm M, Babina M, Hompes S. Causes and risk factors for anaphylaxis. J Dtsch Dermatol Ges. 2013 Jan;11(1):44-50. doi: 10.1111/j.1610-0387.2012.08045.x. Epub 2012 Nov 26.

[32] Kastner M, Harada L, Waserman S. Gaps in anaphylaxis management at the level of physicians, patients, and the community: a systematic review of the literature. Allergy 2010;65:435-44

[33] Alrasbi M, Sheikh A. Comparison of international guidelines for the emergency medical management of anaphylaxis. Allergy 2007;62:838-41

[34] Dhami S, Panesar SS, Roberts G, Muraro A, Worm M, Bilò MB, Cardona V et al; EAACI Food Allergy and Anaphylaxis Guidelines Group Management of anaphylaxis: a systematic review. Allergy. 2014 Feb;69(2):168-75. doi: 10.1111/all.12318. Epub 2013 Nov 20.

[35] Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy
2000;30:1144-50

[36] Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. Cochrane Database Syst Rev 2008;CD006312.

[37] Sheikh A, Ten Broek V, Brown SGA, Simons FER. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. Allergy 2007;62:830-7

[38] Choo KJL, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. Cochrane Database Syst Review 2012;4:CD007596

[39] Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunol Allergy Clin North Am 2007;27:309-26

[40] Epipen demonstration video http://www.youtube.com/watch?v=kv8ORR75UZE

[41] Jext demonstration video http://www.youtube.com/watch?v=3dm8kleUUXo

[42] Kemp SF. Current concepts in pathophysiology, diagnosis, and management of anaphylaxis. Immunol Allergy Clin North Am 2001;21:611-634

[43] Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol 2002;110:341-348

[44] Joint Task Force on Practice Parameters. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998; 101:S465-S527

[45] Dhami S, Zaman H, Varga EM, Sturm GJ, Muraro A, Akdis CA et al. Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis. Accepted in Allergy 31 October 2016

[46] Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Accepted for publication by Allergy 3January 2017

[47] Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol. 2002 Jul;110(1):174-82.